Please cancelled claims 20 and 21 without prejudice or declaimer.

REMARKS

Claims 1-4, and 7-10 have been amended for clarity purposes. No new matter has been added to these claims. Claims 20 and 21 have been cancelled.

Claims 1-4, 7-10, 20, and 21 stand rejected under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The amendments to the claims and the arguments presented herewith overcome these rejections.

The Examiner rejected claims 1-4 and 7-10 as indefinite for "reciting an improper Markush groups for alternative limitations in the claims." Independent claim 1 has been amended to remove the alternative expressions in the claim. As amended, a Markush expression is no longer needed for claim 1. Claim 3 has been amended to place the claim in proper Markush format. Therefore, as amended, claims 1-4 and 7-10 are no longer indefinite for reciting improper Markush groups.

The Examiner also rejected claims 1-4 and 7-10 as indefinite for "reciting the terms 'related organism', 'analogous components', 'chemical equivalents', and 'functional equivalents'." Claims 1, 7, and 8, the claims which recite these terms, have been amended to remove these terms. This rejection is, therefore, now moot.

The Examiner further rejected claims 3 and 4 as indefinite for the use of the abbreviation IDDM without identification of the meaning of the abbreviation. The abbreviation IDDM is defined on page 1, line 30, of the specification as the abbreviation for insulin-dependent diabetes mellitis. Claims 3 and 4 have been amended to change the abbreviation IDDM to insulin-dependent diabetes mellitis, in accordance with the specification. Accordingly, this rejection is now moot.

The Examiner rejected claims 2-4 and 7-10 as indefinite for using the term "A method" in the claims. Claims 2-4 and 7-10 have been amended to change "A method" to --The

method--, to add clarify these claims. Accordingly, these amended claims are not indefinite, and this rejection should be withdrawn.

The Examiner rejected claim 7 as indefinite for "the recitation of 'any one of claims 1-6' because it is dependent from a non-elected claim 5 or 6." Claim 7 has been amended to recite "any one of claims 1-4." Claim 7 is no longer dependent upon non-elected claims and is, therefore, no longer indefinite for this reason.

The Examiner rejected claim 9 as indefinite for using the term "derived". Claim 9 has been amended to remove this term from the claim. Accordingly, amended claim 9 is no longer indefinite, and this rejection should be withdrawn.

Claims 20 and 21 stand rejected as indefinite for "not setting forth any steps involved in the method/process. . . ." Both claims 20 and 21 have been cancelled, making this rejection moot.

Claims 20 and 21 also stand rejected under 35 USC 101 "because the claimed recitation of a use, without setting forth any steps involved in the process, result in an improper definition of a process. . . ." Again, the cancellation of claims 20 and 21 make this rejection moot.

Claim 10 stands rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is respectfully traversed, and reconsideration is requested. The Examiner states: "Claim 10 is directed to a method of immunomodulatory therapy in a human by administering a cell wall component of *Mycobacterium* to the human. However, the specification does not sufficiently establish that the method can be used as claimed. Applicant's only evidence of immunomodulatory therapy is the mice test and there is insufficient evidence that such studies correlate with efficacy in a human."

The use of carefully selected animal models to study human diseases is well established. Laboratory animals play an important role not only as biological models for the study of the physiological and metabolic functions in the human body, but also as disease models for

understanding the mechanism(s) of human diseases. The use of animal models for human diseases is required by the FDA before they are trialed in humans. Further, a Medline search of animal models of disease resulted in 14,560 reference hits. Accordingly, both the FDA, and those in the art, recognize that animal models can be effectively used to model diseases in humans. The most powerful approach to utilize animal models to determine the bases of human diseases, is the identification and functional analysis of genes in model organisms, predominantly mice.

As stated in Applicant's specification page 2, lines 3-11, and the references cited therein, the use of non-obese mice as a valuable model in studying IDDM is known in the art. NOD mice are used because these mice spontaneously develop the disease which has many immunological and pathological similarities to human IDDM.

The similarities include:

- the histology of insulitis;
- the cellular and humoral immune responses specific for beta-cell antigens. These antigens include insulin, GAD65, GAD67, carboxypeptidase H (CPH), peripherin, a 37-kDa secretory granule protein, heat shock protein (HSP) 60, and a 69-kDa islet cell antigen;
- susceptibility genes associated with certain haplotypes of the major histocompatibility complex (MHC) [Singer et al, Diabetes 47:1570-77 1998] and
- the functional and numerical deficit in a small population of lymphocytes called NKT cells.

These known similarities show that treatment options found useful in NOD mice can be used to project treatment options in human subjects. Accordingly, the withdrawal of the rejection of claim 10, under 35 USC 112, first paragraph, is appropriate.

Claims 1-4 and 7-9 stand rejected under 35 USC 102(b) as being anticipated by Qin. This rejection is traversed, and reconsideration is requested. The Examiner states that Qin "teaches a method of immunomodulatory therapy for the treatment of the autoimmune disease

insulin-dependent diabetes mellitus (IDDM) in a mouse comprising administering the components of cell wall of *Mycobacterium bovis* (Abstract).

In Qin, the efficacy (as defined as protection from spontaneous IDDM in NOD mice) of the following compounds were studied:

- complete Freund's Adjuvant (CFA), an oil/saline emulsion, containing whole killed Mycobacterium tuberculosis;
- MDP (Sigma), Muramyl dipeptide, or N-acetylmuramyl-L-alanyl-D-isoglutamine, a peptidoglycan immunoadjuvant originally isolated from bacterial cell wall fragments;
- BCG, (bacillus Calmette-Guerin), an attenuated strain of *Mycobacterium bovis,* administered whole and live.

Qin taught that the use of CFA and BCG was effective, as previously published by others, and as described in the Background of the Invention page 2, lines 7-8 of the application. Applicant does not claim the use of whole organisms. Applicant claims only the use of effective cell wall components of *Mycobacterium.* Qin discusses the use of MDP, a compound derived from bacterial cell wall fragments. However, Qin found that MDP did not prevent the onset of diabetes. Likewise, GMDP, a cell wall component structurally similar MDP, was found by Applicant not to prevent diabetes. In claims 1-4 and 7-9, Applicant does not claim the use of the ineffective cell wall components MDP and GMDP. Since Qin does not teach immunomodulatory therapy using effective cell wall components, claims 1-4 and 7-9 are patentable over Qin.

Claims 1-3 and 7-10 stand rejected under 35 USC 102(b) as being anticipated by Robinson. This rejection is respectfully traversed, and reconsideration is requested. The Examiner states that Robinson teaches "a method of immunomodulatory therapy in a human comprising administering the components of cell wall of *Mycobacterium* (Abstract)."

In Robinson, the authors performed *in vitro* experiments examining certain characteristics of material described as "the delipidified component of the insoluble portion of *Mycobacterium leprae*". These experiments included:

- induction of proliferation *in vitro* of leucocytes from leprosy patients;
- demonstrating that antibodies from leprosy patients could bind it *in vitro*;
- demonstrating that such antibodies could interfere with proliferation *in vitro* of leucocytes from leprosy patients stimulated with the material; and
- factors released from *in vitro* cultures of leucocytes from leprosy patients with the material stimulated macrophages to kill *M.leprae* organisms *in vitro*.

Robinson, therefore only describes the *in vitro* administration of components of *Mycobacterium* cell wall, not the *in vivo* administration of components of *Mycobacterium* cell wall as disclosed and claimed by Applicant.

Further, persons of ordinary skill in the art will recognize the difference between the vaccination method taught by Robinson and the immunomodulation method claimed by Applicant. With vaccination, the specificity of the immune response induced is directed against the organism by virtue of the vaccine expressing immunogenic epitopes that belong to that organism. Robinson discusses the administering a sub-component of an organism, in order to stimulate an immune response against the organism, which is called vaccination. The present invention is distinguished from vaccination in that the present invention is directed to immunomodulation of one response (the autoimmune response, for example) by treatment with an agent unrelated to the target tissue.

The difference between the vaccination approach described in Robinson, and the immunomodulation approach claimed by Applicant, is demonstrated by the failure of killed *M. leprae* to stimulate leucocytes from leprosy patients in the Robinson paper (See Robinson, page 173, column 1, paragraph 3). In contrast, Applicant has shown that BCG was able prevent the onset of autoimmune diabetes (See Figure 3). That is, the effect of the immunomodulation approach described in the patent application is shared by whole organisms and cell wall fragments, and is enriched within the cell wall fragment and especially in MAPG. In contrast, the effect described by Robinson and Mahadevan was not seen in the whole organism until the protein immune targets were revealed by delipidification. Since Applicant claims a method of

immunomodulation not a method of vaccination as described in Robinson, claims 1-3 and 7-10 are patentable over Robinson.

For the foregoing reasons, early action allowing the claims in this application is solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made**".

In the event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 229752000600. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: June 14, 2001

By: _____

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

1. (Amended) A method of immunomodulatory therapy in a mammal said method comprising administering to said mammal an immunomodulating effective amount of one or more components of the cell wall of *Mycobacterium* ~~or a related organism or analogous components from another biological source or chemical equivalents of said components~~.

2. (Amended) ~~A~~ The method according to claim 1 wherein the immunomodulatory therapy is for the treatment of an autoimmune disease.

3. (Amended) ~~A~~ The method according to claim 2 wherein the autoimmune disease is ~~one or more of~~ insulin-dependent diabetes mellitis ~~IDDM~~, thyroiditis, atrophic gastritis (type A), pernicous anaemia, Addison's disease, pemphigus vulgaris, pemphigoid, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, discoid lupus erythematosus, haemolytic anaemia, sympathetic ophthalmia, uveitis, idiopathic thrombocytopenia, idiopathic leucopenia, primary biliary cirrhosis, autoimmune chronic active hepatitis, ulcerative colitis, Sjogren's syndrome, dermatomyositis, scleroderma ~~and~~ or mixed connective tissue disease.

4. (Amended) ~~A~~ The method according to claim 3 wherein the autoimmune disease is insulin-dependent diabetes mellitis~~IDDM~~.

7. (Amended) ~~A~~ The method according to any one of claims 1 to ~~6~~ 4 wherein the cell wall component comprises mycolyl-arabinogalactan-peptidoglycan (MAPG) or a component thereof ~~or chemical equivalent thereof~~ with or without other associated cell wall components and submolecular components ~~or their chemical equivalents~~.

8. (Amended) ~~A~~ The method according to claim 7 wherein MAPG is administered in combination with one or more of mycolic acids, peptidoglycan or arabinogalactan ~~or chemical or functional equivalents thereof~~.

9. (Amended) ~~A~~ The method according to claim 7 wherein MAPG or its components are ~~derived~~ from *Mycobacterium bovis*.

10. (Amended) ~~A~~ The method according to claim 1 wherein the mammal is a human.

Please cancelled claims 20 and 21 without prejudice or declaimer.